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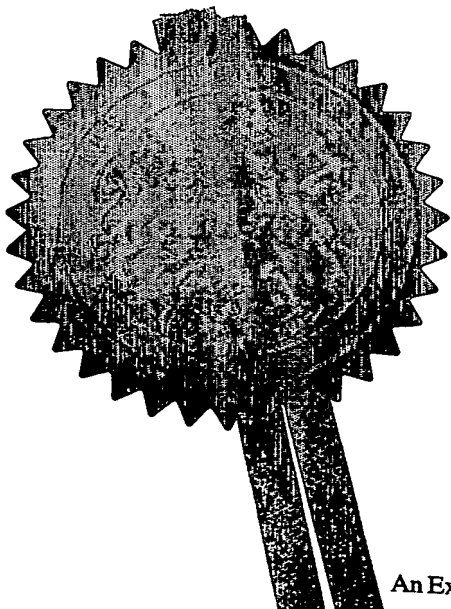
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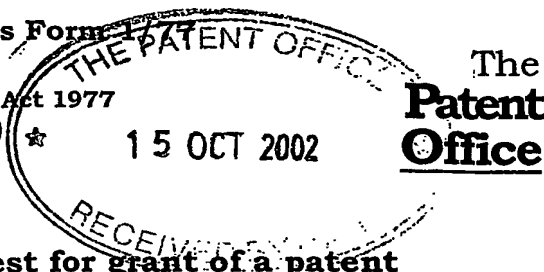
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1 / 77  
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2.	Patent application number (The Patent Office will fill in this part)	0223976.2		
3.	Full name, address and postcode of the or of each applicant (underline all surnames)	BIOCHEMIE GBESELLSCHAFT MBH A-6250 KUNDL TIROL AUSTRIA		
	Patent ADP number (if you know it)	8355158001		
	If the applicant is a corporate body, give the country/state of its incorporation	AUSTRIA		
4.	Title of invention	Organic compounds		
5.	Name of your agent (if you have one)	B.A. YORKE & CO.		
	"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH		
	Patents ADP number (if you know it)	1800001		
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	a) any applicant named in part 3 is not an inventor, or			
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Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

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11. I/We request the grant of a patent on the basis of this application

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Date

B. A. Yorke & Co.

B.A. Yorke & Co.

15 October 2002

12. Name and daytime telephone number of person to contact in the United Kingdom
- Mrs. E. Cheetham  
020 8560 5847

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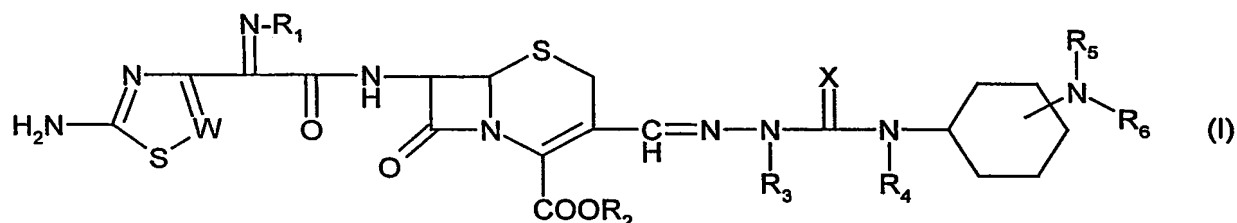
- 1 -

**Organic compounds**

The present invention relates to organic compounds e.g. antimicrobial compounds such as cephalosporines.

5

In one aspect the present invention provides a compound of formula



wherein

10 W is CH or N,

R<sub>1</sub> is hydrogen, hydroxy, (C<sub>1-6</sub>)alkoxy, halo(C<sub>1-6</sub>)alkoxy, hydroxycarbonyl(C<sub>1-6</sub>)alkoxy or (C<sub>1-6</sub>)alkyloxycarbonyl(C<sub>1-6</sub>)alkoxy,

R<sub>2</sub> is hydrogen or an ester moiety,

R<sub>3</sub> is hydrogen, (C<sub>1-6</sub>)alkyl, allyl or cyclo(C<sub>3-8</sub>)alkyl,

15 R<sub>4</sub> is hydrogen or methyl,

R<sub>5</sub> and R<sub>6</sub> independently from each other are hydrogen, (C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkylcarbonyl, arylcarbonyl, aryl(C<sub>1-6</sub>)alkylcarbonyl, heteroaryl(C<sub>1-6</sub>)alkylcarbonyl, (C<sub>1-6</sub>)alkylsulfonyl, arylsulfonyl or aryl(C<sub>1-6</sub>)alkylsulfonyl, and

20 X is N-R<sub>8</sub>, O, S, O-R<sub>8</sub> or S-R<sub>8</sub> wherein R<sub>8</sub> is hydrogen, (C<sub>1-6</sub>)alkyl, cyclo(C<sub>3-8</sub>)alkyl or aminocyclo(C<sub>3-8</sub>)alkyl.

In a preferred aspect the present invention provides a compound of formula I wherein

W is CH or N,

25 R<sub>1</sub> is hydroxy, methoxy, fluoromethoxy, hydroxycarbonylmethoxy or hydroxycarbonylisopropoxy,

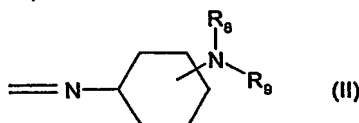
R<sub>2</sub> is hydrogen,

R<sub>3</sub> is hydrogen, methyl, allyl or cyclopropyl,

R<sub>4</sub> is hydrogen or methyl,

- 2 -

$R_5$  and  $R_6$  independently from each other are hydrogen, methyl, phenylcarbonyl, aryl substituted by acetyloxy, phenyloxyacetyl, phenylsulfonyl substituted by amino or acetylamino, 1-thiophene-2-yl-acetyl or cyclohexyl substituted by amino, X is NH, NCH<sub>3</sub>, O, S, S-(C<sub>1-6</sub>)alkyl or a group of formula



wherein  $R_8$  and  $R_9$  have the same meaning as  $R_5$  and  $R_6$ .  
 $NR_5R_6$  and  $NR_8R_9$  can be in o, m or p position.

An ester moiety includes alkyl; e.g. unsubstituted alkyl or substituted alkyl, e.g. by aryl, such as benzyl, alkoxybenzyl, such as 4-methoxybenzyl, alkoxy, such as methoxymethyl; alkyloxycarbonyloxy; alkyl; alkoxy, such as glycyloxy, phenylglycyloxy, e.g. glycyloxymethyl, phenylglycyloxymethyl; heterocyclyl e.g. 5-methyl-2-oxo-1,3-dioxolen-4-yl; indanyl, phthalidyl, alkoxycarbonyloxy and ester moieties which form with the COO<sup>-</sup> group a physiologically hydrolysable and acceptable ester, e.g. such known to be hydrolysable ester groups in the field of cephalosporins. A compound of formula I may thus be in the form of an physiologically-hydrolysable and -acceptable ester. By physiologically-hydrolysable and -acceptable esters as used herein is meant an ester in which the COO<sup>-</sup> group is esterified and which is hydrolysable under physiological conditions to yield an acid which is itself physiologically tolerable at dosages to be administered. The term is thus to be understood as defining regular pro-drug forms. An ester moiety may be preferably a group which is easily hydrolysable under physiological conditions. Such esters may be administered preferably orally. Parenteral administration may be indicated if the ester *per se* is an active compound or, if hydrolysis occurs in the blood.

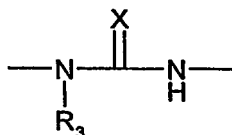
If not otherwise indicated herein any carbon containing group may contain up to 20 carbon atoms. Aryl includes (C<sub>6-18</sub>)aryl, preferably phenyl, naphthyl, e.g. phenyl.

Any group(s) may be unsubstituted or one or morefold substituted, e.g. by groups as conventional in cephalosporine chemistry.

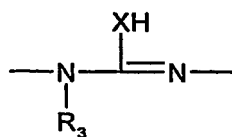
In this specification unless otherwise indicated terms such as "compound of formula I" embrace the compound in any form, for example in the form of a salt and in free base form.

- The present invention thus includes a compound in free base form or, e.g. where such forms exist, in the form of a salt, for example in the form of an acid addition salt, inner salt, quaternary salt and/or in the form of a solvate, for example in the form of a hydrate. A salt may be a pharmaceutically acceptable salt of a compound of formula I such as a metal salt or an amine salt. Metal salts include for example sodium, potassium, calcium, barium, zinc, aluminum salts, preferably sodium or potassium salts. Amine salts include for example trialkylamine, procaine, dibenzylamine and benzylamine salts. The amino group of the cyclohexyl ring in a compound of formula I may be e.g. a  $\text{NH}_3^+$  group,  $\text{NR}_5\text{R}_6\text{R}_7$  or  $\text{NH}_2\text{R}_5$ , wherein  $\text{R}_5$  and  $\text{R}_6$  have the before said meanings and  $\text{R}_7$  independently of  $\text{R}_5$  and  $\text{R}_6$  may have the same meaning as those and may be in m, o or p position. In a preferred embodiment each of  $\text{R}_5$ ,  $\text{R}_6$  and  $\text{R}_7$  is methyl. Counterions are those as conventional, e.g. hydroxy or chloride ions. A free form of a compound of formula I may be converted into a salt form, a solvate form or a salt and a solvate form and *vice versa*.
- In a further aspect the present invention provides a compound of formula I in the form of a salt, for example an acid addition salt or a metal salt; e.g. and a compound of formula I in free form, in the form of a salt, in the form of a solvate or in the form of a salt and a solvate.

- The present invention includes a compound of formula I in any isomeric/tautomeric form in which it may exist. E.g. the configuration in group



may (co)exist in the form of



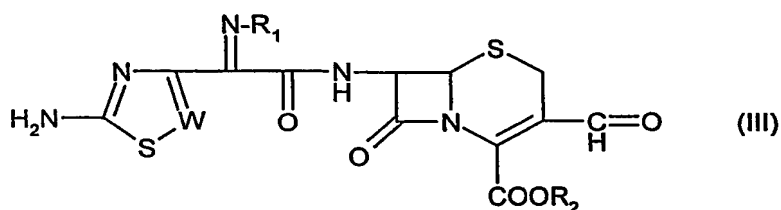
- Also e.g. geometric isomers if  $\text{R}_1$  is other than hydrogen may be syn [(Z)] and anti [(E)] and is preferably syn [(Z)]. E.g. a chiral carbon atom may be introduced, e.g. during a production process of a compound of formula I and corresponding stereoisomeric forms of a compound of formula I may be obtained, e.g. a mixture of the individual stereoisomers, e.g. a racemate, or pure isostereoisomeric forms. Mixtures of isomers may be separated according to a method of conventional.

- 4 -

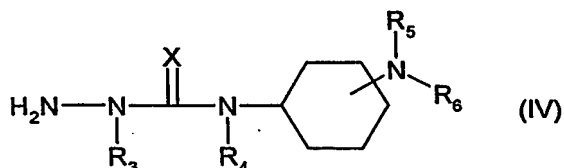
The present invention includes a compound of formula I in any tautomeric form, in any isomeric mixtures and in the form of pure isomers.

Any compound mentioned herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. analogously to a method as conventional or as disclosed herein.

In another aspect the present invention provides a process for the production of a compound of formula I by reacting a compound of formula



wherein  $R_1$  and  $R_2$  are defined as described before, with a compound of formula



wherein  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are defined as described before under appropriate conditions.

If desired, reactive groups may be protected with protecting groups, which may be, or, which are split off under the reaction conditions, or after the reaction. A compound of formula I wherein  $R_2$  is hydrogen may be converted into a compound of formula I wherein  $R_2$  is an carboxylic acid ester group. A compound of formula I may be isolated from the reaction mixture as appropriate, e.g. analogously to a method as conventional.

The compounds of formula I e.g. including salt/solvate, hereinafter designated as "active compound(s) of the invention" exhibit pharmacological activity, e.g. beside low toxicity and are therefore useful as pharmaceuticals. In particular, the active compounds of the invention show antimicrobial, e.g. antibacterial, activity against e.g. gram negative and gram positive bacteria, e.g. gram positive bacteria, such as e.g. *Escherichia*, e.g. *Escherichia coli*; *Enterobacter*, e.g. *Enterobacter cloacae*; *Enterococcus*, e.g. *Enterococcus faecalis*; *Klebsiella*, e.g. *Klebsiella pneumoniae*; *Streptococcus*, e.g. *Streptococcus pneumoniae*;

Staphylococcus, e.g. Staphylococcus aureus; and Pseudomonas, e.g. Pseudomonas aeruginosa, in vitro in the Agar Dilution Test according to National Committee for Clinical Laboratory Standards (NCCLS) 1993, Document M7-A3Vol.13, No. 25: "Methods for dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically -Third Edition, Approved Standard". The active compounds show an MIC ( $\mu\text{g/ml}$ ) in the Agar Dilution Test from about <0.0125 to ca. >6.25. The active compounds of the invention show a surprising overall activity spectrum. The activities for a salt form and/or a solvate form of the compound of formula I are in the same range as the activity of the compound of formula I in free form.

- 10 In another aspect the present invention provides an active compound for use as a pharmaceutical, preferably as an antimicrobial agent, such as an antibiotic.
- In a further aspect the present invention provides an active compound of the present invention for use in the preparation of a medicament for the treatment of microbial diseases, for example diseases mediated by bacterias selected from *Escherichia*, *Enterobacter*,  
15 *Enterococcus*, *Klebsiella*, *Streptococcus*, *Staphylococcus* and *Pseudomonas*.

The present invention provides in further aspects

- an active compound of the present invention for use as a pharmaceutical in the treatment of microbial diseases caused by bacterias selected from *Escherichia*, *Enterobacter*, *Enterococcus*, *Klebsiella*, *Streptococcus*, *Staphylococcus* and *Pseudomonas*; and
- 20 - the use of an active compound of the present invention or the use of a pharmaceutical composition comprising an active compound of the present invention as a pharmaceutical

- In a further aspect the present invention provides a method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective  
25 amount of an active compound of the present invention.

Treatment includes disease treatment as well as prophylactic treatment.

- For this indication, the appropriate dosage will, of course, vary depending upon, for example, the compound of formula I used, the host, the mode of administration and the nature and  
30 severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range from about 0.05 to 5 g, for example 0.1 to about 2.5 g, of an active compound of the invention conveniently administered, for example, in divided doses up to four times a day.



An active compound of the invention may be administered by any conventional route, for example orally, *e.g.* in form of tablets or capsules, or parenterally in the form of injectable solutions or suspensions, *e.g.* in analogous manner to ceftazidime.

- 5 The compound of example 1 is a preferred compound of the present invention.  
It has, for example been determined that the MIC ( $\mu\text{g/ml}$ ) of the compound of Example 1  
against, for example *Klebsiella pneumoniae* is about 0.0125. It is therefore, indicated that for  
the treatment of microbial diseases, *e.g.* bacterial diseases, the preferred compounds of the  
invention may be administered to larger mammals, for example humans, by similar modes of  
10 administration at similar dosages than conventionally used with ceftazidime.

The compounds of formula I may be administered in pharmaceutically acceptable salt form,  
*e.g.* acid addition salt form or base addition salt form or in the corresponding free forms,  
optionally in solvate form. Such salts exhibit the same order of activity as the free forms.

- 15 In another aspect the present invention provides a pharmaceutical composition comprising  
an active compound of the present invention in association with at least one  
pharmaceutically excipient. Such compositions may be manufactured accordingly, *e.g.*  
analogously to a method as conventional. Pharmaceutical excipient(s) include(s)  
20 pharmaceutically active excipient.

In the following examples which illustrate the present invention all temperatures are given in  
degree centigrade. RT means room temperature.

## EXAMPLES

Example 1:**A) SYNTHESIS OF INTERMEDIATE COMPOUNDS****a) Benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a monohydrochloride**

35 g of the benzylidene derivative of S-methyl-2-methyl-isothiosemicarbazide in the form of a hydrochloride and 32.79 g of trans-1,4-diaminocyclohexane in 300 ml of MeOH are refluxed. The mixture obtained is stirred at RT, a precipitate forms, is filtered off and solvent is evaporated. The evaporated residue is treated with 217.5 ml of 2M HCl, a precipitate formed is filtered off, washed and dried. The volume of the filtrate obtained is brought to about 150 ml, a precipitate is formed, filtered off, washed and dried. The dried, combined precipitates are recrystallized from water and the benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a monohydrochloride is obtained.

**b) 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine dihydrochloride**

From a mixture of 24.74 g of benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a monohydrochloride in 79.9 ml of 2M HCl, benzaldehyde is distilled off and solvent from the remaining mixture is evaporated. 3-Amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a dihydrochloride is obtained.

**B) SYNTHESIS OF SUBSTITUTED CEPHALOSPORINES****a) 3-[(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl]-7-[[[(5-amino-[1,2,4]thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino]-3-cephem-4-carboxylic acid trihydrochloride**

To a mixture of 2 g of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a dihydrochloride in 3.4 ml of 2M HCl and 6.1 ml of dimethylacetamide, 2.78 g of N-(1,4,5a,6-tetrahydro-3-hydroxy-1,7-dioxo-3H,7H-azeto(2,1-b)furo(3,4-d)(1,3)-thiazin-6-yl)-2-(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-2-(fluoromethoxyimino) acetic acid amide are added and the suspension obtained is stirred at RT. The mixture obtained is poured into acetonitrile under stirring. A precipitate formed is filtrated off, washed and dried. 3-[(E)[[1-Trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl]-7-[[[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl] amino]-cephem-4-carboxylic acid in the form of a trihydrochloride is obtained.

**b) 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-[[5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid monohydrochloride**

- 10 g of the crude 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-[[5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid in the form of a trihydrochloride are dissolved in 42 ml of water and subjected to chromatography (e.g. LiChroprep RP-18<sup>R</sup>, Merck, grain size 40-63  $\mu$ m). Fractions containing the desired product in the form of a monohydrochloride (HPLC determination) are combined and optionally lyophilised. 3-{(E)[[1-Trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-[[5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid in the form of a monohydrochloride is obtained, optionally as a lyophilizate.
- 15 In the manner as described in Example 1 using the corresponding reactants the following compounds are obtained. Chromatographic purification may be carried out optionally.

**TABLE 1:**

20

**W is N except for ex. 4, 5 and 24 wherein W = CH,**

**R<sub>1</sub> is O-CH<sub>2</sub>-F except for ex.4 wherein R<sub>1</sub> is OH, ex. 5 wherein R<sub>1</sub> is O-CH<sub>3</sub> and for ex. 24 wherein R<sub>1</sub> is O-CH(CH<sub>3</sub>)<sub>2</sub>COOH,**

**R<sub>2</sub> is H,**

25 **R<sub>3</sub> is H for ex. 7-11, 14-18, CH<sub>3</sub> for ex. 2-5, 12-13, 19-28, CH<sub>2</sub>-CH<sub>3</sub> for ex. 3, CH<sub>2</sub>-CH=CH<sub>2</sub> for ex. 6, cyclopropyl for ex.29 and**

**R<sub>4</sub> is H except for ex.14 wherein R<sub>4</sub> is CH<sub>3</sub>, and**

**X, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are as defined in TABLE 1.**

**All compounds are in trans conformation, except example 2 (= cis).**

30 **Position describes the position of the groups N-R<sub>5</sub>R<sub>6</sub> or N-R<sub>5</sub>R<sub>6</sub>R<sub>7</sub> in the cyclohexylring with respect to the R<sub>4</sub>-N group also attached to said cyclohexylring in a compound of formula I.**

Example	X	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	N-R <sub>5</sub> R <sub>6</sub> or N-R <sub>5</sub> R <sub>6</sub> R <sub>7</sub> position
2	NH	H	H	-	p
3	NH	H	H	-	p
4	NH	H	H	-	p
5	NH	H	H	-	p
6	NH	H	H	-	p
7	NH	H	H	-	o
8	NH	H	H	-	p
9	NH	CH <sub>3</sub>	CH <sub>3</sub>	-	p
10	NH	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	p
11	N-CH <sub>3</sub>	H	H	-	o
12	NH	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	p
13	NH	-SO <sub>2</sub> -Phe-NH <sub>2</sub> (p)	-	-	p
14	N-CH <sub>3</sub>	CH <sub>3</sub>	-	-	p
15	N-CH <sub>3</sub>	H	H	-	p
16	N-CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	-	p
17	N-CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	p
18	N-CH <sub>3</sub>	H	H	-	o
19	N-cyclohexyl- NH <sub>2</sub> (p)	H	H	-	p
20	NH	H	H	-	m
21	NH	H	H	-	m
22	NH	H	H	-	m
23	NH	H	H	-	m
24	NH	H	H	-	p
25	S	H	H	-	p
26	O	H	H	-	p
27	NH	H	H	-	m
28	N-CH <sub>3</sub>	H	H	-	p
29	NH	H	H	-	p

**Example 30:**

**3-{(E)[[1-trans-(4-acetylamino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid-dihydrochloride**

- 5 A suspension of 0.2579 g of 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid trihydrochloride in 20 ml of acetonitrile is dissolved with 0.6395 g of N,O-bis-(trimethylsilyl)-acetamid. After adding 0.026 ml of acetylchloride and stirring, 0.115 ml of water are added. A precipitate formed is filtered, washed and dried
- 10 and 3-{(E)[[1-trans-(4-acetylamino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-[(Z)-fluoromethoxyimino]-acetylamino}-cephem-4-carboxylic acid in the form of a dihydrochloride is obtained.

- In the manner as described in example 30 and using the corresponding reactants the
- 15 following compounds are obtained:

**TABLE 2:**

W is N, R<sub>1</sub> is O-CH<sub>2</sub>-F, R<sub>2</sub> is H, R<sub>3</sub> is CH<sub>3</sub> and R<sub>4</sub> is H and X, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are as defined in TABLE 2.

- 20 Position describes the position of the groups N-R<sub>5</sub>R<sub>6</sub> or N-R<sub>5</sub>R<sub>6</sub>R<sub>7</sub> in the cyclohexylring with respect to the R<sub>4</sub>-N group also attached to said cyclohexylring in a compound of formula I.

Example	X	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	N-R <sub>5</sub> R <sub>6</sub> R <sub>7</sub> position
31	NH	-CO-phe	-	-	p
32	NH	-CO-phe-OCOCH <sub>3</sub> (o)	-	-	p
33	NH	-CO-CH <sub>2</sub> -O-phe	-	-	p
34	NH	-SO <sub>2</sub> -phe-NHCOCH <sub>3</sub> (p)			p
35	NH	-CO-CH <sub>2</sub> -thiophene(2)	-	-	p

## Example 36

**3-{(E)[[(trans-4-aminocyclohexylimino)methylthiomethyl]methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid**

- 5 a) **3-{(E)[[(trans-4-((1,1-dimethylethoxy)carbonyl)aminocyclohexylimino) methylthio-  
methyl]methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-  
(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid**

To a solution of 0.144 g of N-(1,4,5a,6-tetrahydro-3-hydroxy-1,7-dioxo-3 H,7 H-azeto(2,1-b)furo(3,4-d)(1,3)-thiazin-6-yl)-2-(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-2-(fluoromethoxyimino)  
10 acetic acid amide in 0.5 ml of dimethylacetamide a solution of 0.103 g of [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester in 2.5 ml of dimethylacetamide is added. After stirring at RT 0.165 ml of 2N HCl are added and a mixture formed is stirred at RT. The mixture obtained is poured onto tert-butyl-methyl-ether and stirred at RT.

15 A precipitate obtained is filtered, washed and dried. 3-{(E)[[(trans-4-((1,1-dimethylethoxy)carbonyl)aminocyclohexylimino)methylthiomethyl]methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid in the form of a hydrochloride is obtained.

- 20 b) **3-{(E)[[(trans-4-aminocyclohexylimino)methylthiomethyl]methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid**

After cooling a suspension of 0.235 g of 3-{(E)[[(trans-4-((1,1-dimethylethoxy)carbonyl)aminocyclohexylimino)methylthiomethyl]methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid hydrochloride  
25 in 2 ml of dichloromethane to 0°C 2 ml of trifluoroacetic acid are added. After stirring a solution obtained, solvent is evaporated, a residue formed is treated with water and a precipitate formed is filtered. After lyophilizing a filtrate the residue obtained is treated with water and 2N HCl. The solution formed is subjected to a chromatography column (e.g. Li  
30 Chroprep RP-18<sup>R</sup>, Merck), fractions containing the desired compound (determined by HPLC) are combined and lyophilised.

3-{(E)[[(Trans-4-aminocyclohexylimino)methylthiomethyl]methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid in the form of a hydrochloride is obtained.

**Example 37:****SYNTHESIS OF INTERMEDIATE COMPOUNDS****Procedure A****3-amino-1-(trans-4-aminocyclohexyl)-guanidine dihydrochloride****5 a) [trans-4-(3-ethoxycarbonyl-thioureido)cyclohexyl]carbamic acid tert-butyl ester**

To a solution of 1.10 g of (4-amino-cyclohexyl)-carbamic acid tert-butyl ester in 25 ml of acetic acid ethyl ester 0.58 ml of ethoxycarbonyl-isothiocyanat are added and stirred at RT. The precipitate formed is filtered and washed with diethylether to give [trans-4-(3-ethoxycarbonyl-thioureido)cyclohexyl]carbamic acid tert-butyl ester.

**10 b) [trans-4-thioureido-cyclohexyl]-carbamic acid tert-butyl ester**

To a suspension of 1.69 g of [trans-4-(3-ethoxycarbonyl-thioureido)cyclohexyl]carbamic acid tert-butyl ester in 10 ml of water and 15 ml of ethanol 7.4 ml of 4M NaOH are added. The resulting mixture is kept at 90°C for 30 minutes. The precipitate formed at RT is filtered and washed with diethylether. (Trans-4-thioureido-cyclohexyl)-carbamic acid tert-butyl ester are obtained.

**15 c) [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester hydroiodide**

A mixture of 1.19 g of (trans-4-thioureido-cyclohexyl)-carbamic acid tert-butyl ester and 0.41 ml of methyl iodide in 50 ml of MeOH is stirred at RT. Solvent is evaporated to give 2.06 g of [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester hydroiodide.

**20 d) [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester hydrochloride**

To a suspension of 2.06 g of [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester in the form of a hydroiodide in 50 ml of water 40 ml of a strong basic ion exchanger in chloride form (Amberlite IRA 400 (Cl)<sup>R</sup>) are added. After stirring the mixture at RT the ion exchanger is filtered and the filtrate is lyophilised to give [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester in the form of a hydrochloride

**25 e) [trans-4-((hydrazino)iminomethyl)aminocyclohexyl]-carbamic acid tert-butyl ester hydrochloride**

To a solution of 1.11 g of [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester in 50 ml of EtOH 0.183 ml of hydrazine monohydrate are added. After refluxing the reaction mixture solvent is evaporated and [trans-4-(hydrazino)iminomethyl)aminocyclohexyl]-carbamic acid tert-butyl ester in the form of a hydrochloride is obtained.

**30 f) 3-amino-1-(trans-4-aminocyclohexyl)-guanidine dihydrochloride**

A reaction mixture of 1.15 g of [trans-4-(hydrazino)iminomethyl)-aminocyclohexyl]-carbamic acid tert-butyl ester in the form of a hydrochloride and 4.2 ml of 5.4M HCl (in MeOH) in

50 ml of MeOH is stirred at RT. The volume of the mixture is reduced and a precipitate formed is filtered to give 3-amino-1-(trans-4-aminocyclohexyl)-guanidine in the form of a dihydrochloride.

- 5 In the manner as described in procedure A, but using the corresponding reactants the following compounds are obtained:

**TABLE 3:**

Example	compound formula
A2	
A3	
A4	
A5	

10 **Procedure B**

**3-amino-2-(trans-4-dimethylaminocyclohexyl)-1-methyl-guanidine dihydrochloride**

**a) 1-(trans-4-dimethylaminocyclohexyl)-3-methyl-thiourea**

To a solution of 1.74 g of trans-4-dimethylaminocyclohexanamine in 50 ml of acetic acid ethyl ester 0.90 g of methyl-isothiocyanate are added. After stirring the mixture obtained at RT solvent is evaporated and 1-(4-dimethylaminocyclohexyl)-3-methyl-thiourea is obtained.

**b) 1-(trans-4-dimethylaminocyclohexyl)-2,3-dimethyl-isothiurea hydrochloride**

A mixture of 0.50 g of 1-(4-dimethylaminocyclohexyl)-3-methyl-thiourea in 10 ml of MeOH, after adding 1.16 ml of 2M HCl (in methanol) and 0.36 g of methyl iodide is stirred at RT.



Solvent is evaporated and a residue formed is taken up in water. 10 ml of a strong basic ion exchanger in chloride form (Amberlite IRA 400 (Cl)<sup>R</sup>) are added. After stirring the mixture at RT a filtrate is lyophilised to give 1-(4-dimethylamino cyclohexyl)-2,3-dimethyl-isothiurea in the form of a hydrochloride.

5 **c) 3-amino-2-(trans-4-dimethylaminocyclohexyl)-1-methyl-guanidine dihydrochloride**

A solution of 0.71 g of 1-(4-dimethylaminocyclohexyl)-2,3-dimethyl-isothiurea hydrochloride in 40 ml of EtOH absolute and 0.126 ml of hydrazine monohydrate is refluxed. Solvent is then evaporated and 3-amino-2-(trans-4-dimethylaminocyclohexyl)-1-methyl-guanidine in the form of a dihydrochloride is obtained.

10

In the manner as described in procedure B, but using the corresponding reactants the following compounds may be obtained:

**TABLE 4:**

15

Example	compound formula
B2	
B3	

**Procedure C**

**[trans-4-((hydrazino)methyliminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride hydrochloride**

20 **a) [trans-4-(2,3-dimethyl-isothioureido)-cyclohexyl]-trimethyl-ammonium hydrochloride**

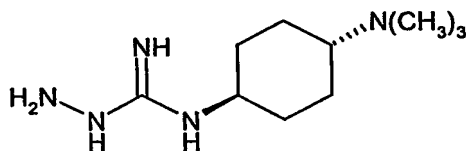
A mixture of 0.50 g of 1-(4-dimethylamino-cyclohexyl)-3-methyl-thiourea in 20 ml of MeOH and 0.36 ml of methyl iodide is stirred at RT. After refluxing a mixture obtained, solvent is evaporated. A residue formed is taken up in water, stirred over a strong basic ion exchanger in chloride form (Amberlite IRA 400 (Cl)<sup>R</sup>), filtered and lyophilised to give [trans-4-(2,3-dimethyl-isothioureido)-cyclohexyl]-trimethyl-ammonium in the form of a hydrochloride.

25

**b) [trans-4-((hydrazino)methyliminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride hydrochloride**

A solution of [trans-4-(2,3-dimethyl-isothioureido)-cyclohexyl]-trimethyl-ammonium hydrochloride in ethanol after adding 0.118 ml of hydrazin monohydrate is refluxed and solvent is evaporated. [Trans-4-((hydrazino)methyliminomethyl)aminocyclo hexyl]-trimethyl-ammonium chloride in the form of a hydrochloride is obtained.

In the manner as described in procedure C, but using the corresponding reactants the following compound is obtained:



**Procedure D**

**3-amino-bis-1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine trihydrochloride**

**a) Benzylidene derivative of 3-amino-bis-1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine dihydrochloride**

Reacting the benzylidene derivative of S-methyl-2-methyl-isothiosemicarbazide with trans-1,4-diaminocyclohexane in the manner already described for the preparation of the benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a monohydrochloride yields the benzylidene derivative of 3-amino-bis 1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine trihydrochloride (determined by HPLC at 254 nm) as a side product. This side product is purified by e.g. column chromatography (Li Chroprep RP-18<sup>R</sup>, Merck). Enriched samples of benzylidene derivative of 3-amino-bis-1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine dihydrochloride are dissolved in water, poured on the column and eluated. Fractions containing the desired product (determined by HPLC) are combined and solvent is evaporated. Benzylidene derivative of 3-amino-bis-1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a dihydrochloride is obtained.

**b) 3-amino-bis-1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine-trihydrochloride**

Removing the benzylidene protecting group proceeds in the same manner already described for 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a dihydrochloride.

In the manner as described in procedure D, but using the corresponding reactants the following compounds may be obtained:

5

**TABLE 5:**

Example	compound formula
D2-D5 und D8	
D6	
D7	

**Procedure E**

- 10 **[trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride hydrochloride**

a) **Benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine**

The pH of a solution of 5 g of the benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a monohydrochloride in of water is adjusted to pH

- 15 13.6 by adding 8N NaOH. The mixture obtained is extracted with dichloromethane. The organic phase is dried and solvent is evaporated to give a benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine.

**b) Benzylidene derivative of [trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride**

To a solution of 1 g of the benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in acetonitrile 1.295 g of methyl iodide in 10 ml of acetonitrile are added. The mixture obtained is refluxed and stirred at RT. Solvent is evaporated, the residue is taken up in water and treated with 20 ml of a strong basic ion exchanger in chloride form (Amberlite IRA 400 (Cl)<sup>R</sup>). A suspension formed is stirred at RT, filtered and a filtrate formed is lyophilised. The lyophilizate is resolved in water and the pH of the solution is adjusted to 13.4 with 8N NaOH. After extracting with dichloromethane, the water phase is adjusted to pH 2 with 8N HCl and lyophilised. The lyophilisate is dissolved in water, subjected to e.g. a chromatography column filled with RP-18<sup>R</sup> (Li Chroprep RP-18<sup>R</sup>, grain size 40-63 µm, Merck). Fractions (examined by means of analytical HPLC) containing the desired product are collected and lyophilised to obtain benzylidene derivative of [trans-4-((1-methylhydrazino)(imino-methyl)aminocyclohexyl]-trimethyl-ammonium chloride.

**c) [trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride hydrochloride**

A mixture of benzylidene derivative of [trans-4-((1-methylhydrazino)(iminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride in 1.7 ml of 2N HCl and water is treated by steam distillation. After evaporation of solvent [trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride hydrochloride is obtained.

**Procedure F**

**3-amino-1-(trans-4-aminocyclohexyl)-3-ethyl-guanidine dihydrochloride**

**a) Benzylidene derivative of [trans-4-((hydrazino)iminomethyl)aminocyclohexyl]-1-N-formamid**

A mixture of 5.5 ml of acetic anhydride and 11.2 ml of formic acid is stirred at 0°C. A solution of 5.04 g of benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-guanidine (preparation of the free base is done in the same manner described in procedure E a) in 5.6 ml of formic acid is added to the mixed anhydride. After stirring a mixture formed solvent is evaporated. A residue obtained is treated with water and the pH of a solution formed is adjusted to 13.02 with 2N NaOH. A precipitate formed is filtered off, washed and dried to give the benzylidene derivative of [trans-4-((hydrazino)iminomethyl)aminocyclohexyl]-1-N-formamid.

**b) Benzylidene derivative of [trans-4-((1-ethylhydrazino)iminomethyl)aminocyclohexyl]-1-N-formamid hydroiodide**

After adding 0.28 ml of ethyliodide to a solution of 0.5 g of the benzylidene derivative of [trans-4-((1-hydrazino)(iminomethyl)aminocyclohexyl]-N-formamid the mixture is refluxed.

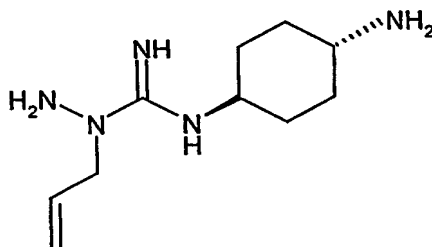
- 5 Keeping the mixture over night at RT and adding ethyliodide following by refluxing the mixture and again keep the resulting mixture at RT results in a precipitate, which is filtered and dried. Benzylidene derivative of [trans-4-((1-ethylhydrazino)iminomethyl)aminocyclohexyl]-1-N-formamid in the form of a hydroiodide is obtained.

**c) 3-amino-1-(trans-4-aminocyclohexyl)-3-ethyl-guanidine dihydrochloride**

- 10 A suspension of 0.34 g of benzylidene derivative of [trans-4-((1-ethylhydrazino)iminomethyl)aminocyclohexyl]-1-N-formamid hydroiodide in 10 ml of water and 10 ml of strong basic ion exchanger in chloride form (Amberlite IRA 400 (Cl)<sup>R</sup>) is stirred. After filtration and adding 2 ml of 2N HCl to the filtrate benzaldehyde is distilled. Solvent is evaporated and 3-amino-1-(trans-4-aminocyclohexyl)-3-ethyl-guanidine in the form of a dihydrochloride is obtained.

15

In the manner as described in procedure F, but using the corresponding reactants the following compound is obtained:



20 **Procedure G**

**4-amino-N-[trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-benzene-sulfonamide dihydrochloride**

**a) Benzylidene derivative of N-[4-[trans-4-((1-methylhydrazino)iminomethyl)] aminocyclohexylsulfamoyl]-phenyl]-acetamid**

- 25 To a suspension of 0.5 g of benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in acetonitrile 2.37 ml of N,O-bis-(trimethylsilyl)-acetamide are added. A solution obtained is treated with 0.378 g of 4-acetylamino-benzenesulfonyl chloride and stirred at RT. After adding of 3.49 ml of water/acetonitrile a precipitate formed is filtered and

washed. The benzylidene derivative of N-[4-[-trans-4-((1-methylhydrazino) iminomethyl)] aminocyclohexylsulfamoyl]-phenyl]-acetamid is obtained.

**b) 4-amino-N-[trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-benzene-sulfonamide dihydrochloride**

- 5 From a suspension of 0.62 g of benzylidene derivative of N-[4-[-trans-4-((1-methylhydrazino) iminomethyl)] aminocyclohexylsulfamoyl]-phenyl]-acetamid 3.4 ml of 1N HCl and water, benzaldehyde and acetic acid is split off. An aqueous solution obtained is concentrated and dried. 4-Amino-N-[trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-benzene-sulfonamide in the form of a dihydrochloride is obtained.

10

**Procedure H**

**3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine dihydrochloride**

**a) [trans-4-(3-amino-3-methyl-thioureido)cyclohexyl]-carbamic acid tert-butyl ester**

- 15 To a solution of 2 g of (trans-4-isothiocyanate-cyclohexyl)-carbamic acid tert-butyl ester 0.49 ml of methylhydrazine are added. After stirring at RT petrolether is added. A precipitate formed is filtered, washed and dried. [Trans-4-(3-amino-3-methyl-thioureido) cyclohexyl]-carbamic acid tert-butyl ester is obtained.

**b) [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester hydrochloride**

- 20 A suspension of 1.17 g of [trans-4-(3-amino-3-methyl-thioureido)cyclohexyl]-carbamic acid tert-butyl ester in 30 ml of MeOH is treated with 0.34 ml of methyl iodide. After refluxing solvent is evaporated. A residue obtained is suspended in water and treated with a strong basic ion exchanger in chloride form (Amberlite IRA 400 (Cl)<sup>R</sup>). After stirring at RT the ion exchanger is filtered off and the filtrate is lyophilised. [Trans-4-(3-amino-2,3-dimethyl-
- 25 isothioureido) cyclohexyl]-carbamic acid tert-butyl ester in the form of a hydrochloride is obtained.

**c) Benzylidene derivative of [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester hydrochloride**

- 30 To a solution of 0.40 g of [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester hydrochloride in 20 ml of water and 30 ml of acetonitrile 1.3 ml of 2N HCl and 0.15 ml of benzaldehyde is added. After stirring the mixture acetonitrile is evaporated and a solution obtained is extracted with ether. After adjusting the pH of the aqueous phase to 7 a precipitate formed is filtered, washed and dried. The benzylidene derivative of [trans-

4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester in the form of a hydrochloride is obtained.

**d) Benzylidene derivative of [trans-4-(1-methylhydrazino)(methyliminomethyl) aminocyclohexyl]-carbamic acid tert-butyl ester**

- 5 A suspension of 0.2 g of benzylidene derivative of [trans-4-(3-amino, 2,3-dimethyl-isothioureido)-cyclohexyl]-carbamic acid tert-butylester hydrochloride is treated with 0.126 of methylamine and stirred. Solvent is evaporated from the clear solution and benzylidene derivative of [trans-4-(1-methylhydrazino)(methyl iminomethyl)aminocyclohexyl]-carbamic acid tert-butylester is obtained.

10 **e) Benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine trifluoroacetate**

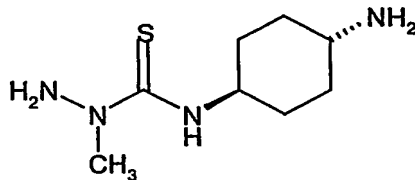
- To a solution of 0.2 g of the benzylidene derivative of [trans-4-(1-methylhydrazino)(methyl-iminomethyl)aminocyclohexyl]-carbamic acid tert-butyl ester in 10 ml of dichloromethane at 0°C 10 ml of trifluoroacetic acid are added. After stirring at RT solvent is evaporated and the benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine trifluoroacetate is obtained.

**f) 3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine dihydrochloride**

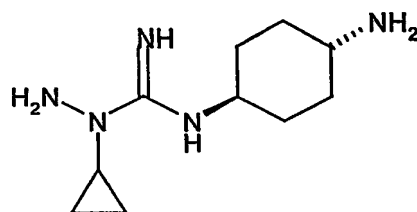
- From a solution of 0.2 g of benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine trifluoroacetate in water and after addition of 1.6 ml of 1N HCl benzaldehyde is splitted off. After reducing the volume of the resulting mixture 20 ml of strong basic ion exchanger in chloride form (Amberlite IRA 400 (Cl)<sup>R</sup>) are added. After stirring, filtration and evaporation of solvent 3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine in the form of a dihydrochloride is obtained.

25

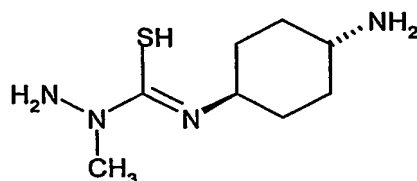
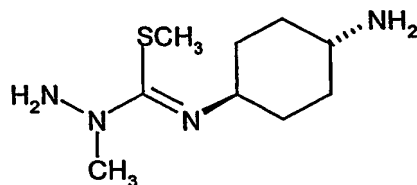
In the manner as described in procedure H, but using the corresponding reactants the following compounds are obtained:



- 21 -



(tert-Butyloxycarbonyl protecting group in procedure H a) is removed with HCl in MeOH)



5

(tert-Butyloxycarbonyl protecting group is removed with trifluoroacetic acid)

### Procedure I

#### **[3-amino-1-(trans-4-aminocyclohexyl)-3-methyl]-urea dihydrochloride**

##### 10 a) [trans-4-(3-amino-3-methyl-ureido)cyclohexyl]-carbamic acid tert-butyl ester

A solution of 0.435 g [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester hydrochloride is treated with 0.18 ml of ammonia (2M in EtOH) and the mixture obtained is refluxed. After stirring at RT solvent is evaporated and [trans-4-(3-amino-3-methyl-ureido)cyclohexyl]-carbamic acid tert-butyl ester is obtained.

##### 15 b) [3-amino-1-(trans-4-aminocyclohexyl)-3-methyl]-urea dihydrochloride

A mixture of 0.34 g of [trans-4-(3-amino-3-methyl-ureido)cyclohexyl]-carbamic acid tert-butyl ester in 15 ml of MeOH and 2 ml of 2N HCl (in MeOH) is stirred at RT for 4 hours. After evaporation of solvent a residue formed is taken up in water, the pH is adjusted to 2 with 2N HCl and a precipitate formed is filtered. After lyophilising [3-amino-1-(trans-4-aminocyclohexyl)-3-methyl]-urea in the form of a dihydrochloride is obtained.

20



**<sup>1</sup>H-NMR-Spectra**(200 MHz, in DMSO-d<sub>6</sub> unless given otherwise)

- 1 1.30 – 1.70, m, 4H, CCH<sub>2</sub>; 1.80 – 2.10, m, 4H, CCH<sub>2</sub>; 2.88 – 3.10, m, 1H, NCH; 3.32, s,  
5 3H, NCH<sub>3</sub>; 3.42 – 3.70, m, 2H, 1H from SCH<sub>2</sub> and 1H from NCH; 4.25, part of the AB-  
quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H, β-lactam; 5.79, d, J=55 Hz, 2H,  
CH<sub>2</sub>F; 5.75, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 8.10, s, 1H, CH=N; 9.84, d, J=8 Hz,  
1H, NH
- 10 2 1.40 – 2.12, m, 8H, CCH<sub>2</sub>; 3.10 – 3.30, m, 1H, NCH; 3.35, s, 3H, NCH<sub>3</sub>; 3.55 and 4.54,  
AB-quartet, J=18 Hz, 2H, SCH<sub>2</sub>; 3.75 – 3.95, m, 1H, NCH; 5.15, d, J=5 Hz, 1H, β-  
lactam; 5.77, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.78, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 8.12, s,  
1H, CH=N; 9.86, d, J=8 Hz, 1H, NH
- 15 3 1.06, t, J=5 Hz, 3H, CH<sub>3</sub>; 1.32 – 1.70, m, 4H, CCH<sub>2</sub>; 1.75 – 2.12, m, 4H, CCH<sub>2</sub>; 2.88 –  
3.10, m, 1H, NCH; 3.48 – 3.72, m, 2H, 1H from SCH<sub>2</sub> and 1H from NCH; 3.98, m, 2H,  
NCH<sub>2</sub>; 4.24, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.14, d, J=5 Hz, 1H, β-lactam;  
5.79, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.77, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 8.12, s, 1H,  
20 CH=N; 9.84, d, J=8 Hz, 1H, NH
- 4 (in D<sub>2</sub>O) 1.28 – 1.65, m, 4H, CCH<sub>2</sub>; 1.80 – 2.10, m, 4H, CCH<sub>2</sub>; 2.82 – 3.08, m, 1H,  
NCH; 3.32 – 3.60, m, 2H, 1H from NCH<sub>2</sub> and 1H from SCH<sub>2</sub>; 4.14, part of the AB-  
quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.09, d, J=5 Hz, 1H, β-lactam; 5.69, d, 1H, β-lactam;  
6.65, s, 1H, CH thiazol; 8.21, s, 1H, CH=N
- 25 5 1.35 – 1.68, m, 4H, CCH<sub>2</sub>; 1.78 – 2.12, m, 4H, CCH<sub>2</sub>; 2.82 – 3.06, m, 1H, NCH; 3.35,  
s, 3H, NCH<sub>3</sub>; 3.50 – 3.80, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 3.90, s, 3H, OCH<sub>3</sub>;  
4.58, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H, β-lactam; 5.90,  
dd, J=5 Hz and 8 Hz, 1H, β-lactam; 6.85, s, 1H, CH thiazol; 8.08, s, 1H, CH=N; 9.79,  
30 d, J=8 Hz, 1H, NH
- 6 1.30 – 1.70, m, 4H, CCH<sub>2</sub>; 1.82 – 2.08, m, 4H, CCH<sub>2</sub>; 2.88 – 3.10, m, 1H, NCH; 3.40 –  
3.68, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 4.42 – 4.78, m, 3H, 2H from NCH<sub>2</sub> and  
1H from SCH<sub>2</sub>; 4.92 – 5.35, m, 3H, 1H from β-lactam and 2H from CH<sub>2</sub>=C; 5.52 – 6.04,

m, 4H, 1H from  $\beta$ -lactam, 1H from C-CH=C and 2H from CH<sub>2</sub>F; 8.08, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

- 7 1.15 – 1.50, m, 4H, CCH<sub>2</sub>; 1.60 – 1.82, m, 2H, CCH<sub>2</sub>; 1.88 – 2.20, m, 2H, CCH<sub>2</sub>; 3.00 – 3.30, m, 1H, NCH; 3.45 – 3.75, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 4.52, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.92, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 8.32, s, 1H, CH=N; 9.82, d, J=8 Hz, 1H, NH
- 5
- 10 8 1.28 – 1.62, m, 4H, NCH<sub>2</sub>; 1.78 – 2.12, m, 4H, NCH<sub>2</sub>; 2.88 – 3.12, m, 1H, NCH; 3.40 – 3.70, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 4.48, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.27, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.77, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.90, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 8.28, s, 1H, CH=N; 10.82, d, J=8 Hz, 1H, NH
- 15 9 1.20 – 1.65, m, 4H, CCH<sub>2</sub>; 1.90 – 2.12, m, 4H, CCH<sub>2</sub>; 2.75, b, 6H, NCH<sub>3</sub>; 3.00 – 3.60, m, 3H, 2 from NCH and 1H from SCH<sub>2</sub>; 4.32, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.22, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.79, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.80, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 8.22, s, 1H, CH=N; 9.78, d, J=8 Hz, 1H, NH
- 20 10 1.30 – 1.70, m, 4H, CCH<sub>2</sub>; 1.92 – 2.32, m, 4H, CCH<sub>2</sub>; 3.05, b, 9H, NCH<sub>3</sub>; 3.20 – 3.68, m, 3H, 2H from NCH and 1H from SCH<sub>2</sub>; 4.48, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.94, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 8.30, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH
- 25 11 1.15 – 1.58, m, 4H, CCH<sub>2</sub>; 1.65 – 2.30, m, 4H, CCH<sub>2</sub>; 2.92, s, 3H, NCH<sub>3</sub>; 3.08 – 3.75, m, 3H, 2H from NCH and 1H from SCH<sub>2</sub>; 4.48, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.32, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.77, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.95, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 8.52, s, 1H, CH=N; 9.82, d, J=8 Hz, 1H, NH
- 30 12 1.40 – 1.75, m, 4H, CCH<sub>2</sub>; 1.92 – 2.32, m, 4H, CCH<sub>2</sub>; 3.04, b, 9H, NCH<sub>3</sub>; 3.25 – 3.80, m, 6H, 3H from NCH<sub>3</sub> and 2H from NCH and 1H from SCH<sub>2</sub>; 4.58, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.27, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.96, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 8.07, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH

- 13 1.10 – 1.45, m, 4H, CCH<sub>2</sub>; 1.55 – 1.88, m, 4H, CCH<sub>2</sub>; 2.65 – 2.95, m, 1H, NCH; 3.28, s, 3H, NCH<sub>3</sub>; 3.32 – 3.60, m, 2H, 1H from NH and 1H from SCH<sub>2</sub>; 4.50, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.26, d, J=5 Hz, 1H, β-lactam; 5.77, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.96, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 6.60, d, J=9 Hz, 2H, aromatic-H; 7.42, d, J=9 Hz, 2H, aromatic-H; 8.07, s, 1H, CH=N; 9.75, d, J=8 Hz, 1H, NH
- 14 1.30 – 1.58, m, 2H, CCH<sub>2</sub>; 1.62 – 1.88, m, 4H, CCH<sub>2</sub>; 2.00 – 2.22, m, 2H, CCH<sub>2</sub>; 2.54, s, 3H, NCH<sub>3</sub>; 2.72 – 3.10, m, 7H, 6H from NCH<sub>3</sub> and 1H from NCH; 3.48-3.72, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 4.10, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H, β-lactam; 5.77, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 8.47, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH
- 15 1.30 – 1.70, m, 4H, CCH<sub>2</sub>; 1.72 – 2.10, m, 4H, CCH<sub>2</sub>; 2.70 – 3.10, m, 4H, 3H from NCH<sub>3</sub> and 1H from NCH; 3.35 – 3.70, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 3.50, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H, β-lactam; 5.78, dd, J=55 Hz, 2H, CH<sub>2</sub>F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 8.55, s, 1H, CH=N; 9.85, d, J=8 Hz, 1H, NH
- 16 1.32 – 1.70, m, 4H, CCH<sub>2</sub>; 1.80 – 2.20, m, 4H, CCH<sub>2</sub>; 2.70, b, 6H, NCH<sub>3</sub>; 2.88, d, 3H, NCH<sub>3</sub>; 3.00 – 3.20, m, 1H, NCH; 3.38 – 3.70, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 4.52, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.29, d, J=5 Hz, 1H, β-lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 8.28, b, 2H, NH<sub>2</sub>; 8.63, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH
- 17 1.40 – 1.70, m, 4H, CCH<sub>2</sub>; 1.88 – 2.30, m, 4H, CCH<sub>2</sub>; 2.88, d, 3H, NCH<sub>3</sub>; 3.08, b, 9H, NCH<sub>3</sub>; 3.20 – 3.80, m, 3H, 2H from NCH and 1H from SCH<sub>2</sub>; 4.51, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.29, d, J=5 Hz, 1H, β-lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.95, dd J=5 Hz and 8 Hz, 1H, β-lactam; 8.30, b, 2H, NH<sub>2</sub>; 8.68, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH
- 18 1.10 – 2.22, m, 8H, CCH<sub>2</sub>; 2.90, d, 3H, NCH<sub>3</sub>; 3.08 – 3.32, m, 1H, NCH; 3.40 – 3.80, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 3.54, part of the AB-quartet, J=18 Hz, 1H,

- 25 -

SCH<sub>2</sub>; 5.30, d, J=5 Hz, 1H, β-lactam; 5.77, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.96, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 8.52, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH

- 19 1.30 – 1.75, m, 8H, CCH<sub>2</sub>; 1.80 – 2.20, m, 8H, CCH<sub>2</sub>; 2.80 – 3.20, m, 2H, NCH; 3.28, s, 3H, NCH<sub>3</sub>; 3.40 – 3.75, m, 3H, 2H from NCH and 1H from SCH<sub>2</sub>; 4.20, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.15, d, J=5 Hz, 1H, β-lactam; 5.76, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 5.79, d, J=55 Hz, 2H, CH<sub>2</sub>F; 8.09, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH
- 10 20 1.02 – 2.20, m, 8H, CCH<sub>2</sub>; 2.90 – 3.18, m, 1H, NCH; 3.32, s, 3H, NCH<sub>3</sub>; 3.42 – 3.78, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 3.55, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H, β-lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 8.12, s, 1H, CH=N; 9.82, d, J=8 Hz, 1H, NH
- 15 21 1.10 – 2.22, m, 8H, CCH<sub>2</sub>; 3.00 – 3.18, m, 1H, NCH; 3.35, b, 3H, NCH<sub>3</sub>; 3.45 – 3.82, m, 1.5H, 1H from SCH<sub>2</sub> and 0.5H from NCH; 4.10 – 4.30, m, 0.5H, NCH; 3.54, part of the AB-quartet, J=18 Hz, 0.5H, SCH<sub>2</sub>; 3.62, part of the AB-quartet, J=18 Hz, 0.5H, SCH<sub>2</sub>; 5.12 – 5.22, m, 1H, β-lactam; 5.70 – 5.85, m, 1H, β-lactam; 5.78, d, J=5 Hz, 2H, CH<sub>2</sub>F; 8.10, b, 1H, CH=N; 9.77, d, J=8 Hz, 1H, NH
- 20 22 1.08 – 1.62, m, 4H, CCH<sub>2</sub>; 1.70 – 2.25, m, 4H, CCH<sub>2</sub>; 2.90 – 3.20, m, 1H, NCH; 3.32, b, 3H, NCH<sub>3</sub>; 3.42 – 3.82, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 4.45 – 4.70, m, 1H, SCH<sub>2</sub>; 5.10 – 5.28, m, 1H, β-lactam; 5.65 – 5.90, m, 1H, β-lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 8.10, b, 1H, CH=N; 9.85, d, J=8 Hz, 1H, NH
- 25 23 1.30 – 2.00, m, 7H, CCH<sub>2</sub>; 2.10 – 2.30, m, 1H, CCH<sub>2</sub>; 3.25 – 3.62, m, 5H, 3H from NCH<sub>3</sub>, 1H from NCH and 1H from SCH<sub>2</sub>; 3.98 – 4.18, m, 1H, NCH; 4.53, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.18, d, J=5 Hz, 1H, β-lactam; 5.78, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 5.79, d, J=55 Hz, 2H, CH<sub>2</sub>F; 8.11, s, 1H, CH=N; 9.75, d, J=8 Hz, 1H, NH
- 30 24 1.30 – 1.70, m, 10H, 4H from CCH<sub>2</sub> and 6H from CCH<sub>3</sub>; 1.82 – 2.12, m, 4H, CCH<sub>2</sub>; 2.88 – 3.12, m, 1H, NCH; 3.29, s, 3H, NCH<sub>3</sub>; 3.42 – 3.70, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 4.48, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.32, d, J=5 Hz, 1H, β-

lactam; 5.98, dd, J=5 Hz and 8Hz, 1H,  $\beta$ -lactam; 7.06, s, 1H, CH thiazol; 8.11, s, 1H, CH=N; 9.68, d, J=8 Hz, 1H, NH

- 25 1.22 – 1.70, m, 4H, CCH<sub>2</sub>; 1.82 – 2.18, m, 4H, CCH<sub>2</sub>; 2.88 – 3.18, m, 1H, NCH; 3.45 –  
5 3.80, m, 4H, 3H from NCH<sub>3</sub> and 1H from SCH<sub>2</sub>; 3.96 – 4.28, m, 1H, NCH; 4.48, part of  
the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.25, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.78, d, J=55 Hz,  
2H, CH<sub>2</sub>F; 5.96, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 8.02, s, 1H, CH=N; 9.86, d, J=8  
Hz, 1H, NH
- 10 26 1.30 – 1.60, m, 4H, CCH<sub>2</sub>; 1.70 – 2.05, m, 4H, CCH<sub>2</sub>; 2.80 – 3.05, m, 1H, NCH; 3.18,  
s, 3H, NCH<sub>3</sub>; 3.38 – 3.68, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 4.48, part of the  
AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.22, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.76, d, J=55 Hz, 2H,  
CH<sub>2</sub>F; 5.92, dd, J=5 Hz and 8Hz, 1H,  $\beta$ -lactam; 7.85, s, 1H, CH=N; 9.82, d, J=8 Hz,  
1H, NH
- 15 27 1.10 – 1.65, m, 4H, CCH<sub>2</sub>; 1.72 – 2.25, m, 4H, CCH<sub>2</sub>; 2.88 – 3.18, m, 1H, NCH; 3.32,  
s, 3H, NCH<sub>3</sub>; 3.42 – 3.80, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 4.54, part of the  
AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.17, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.77, dd, J=5 Hz and 8  
Hz, 1H,  $\beta$ -lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 8.10, s, 1H, CH=N; 9.85, d, J=5 Hz, 1H,  
20 NH
- 28 1.28 – 1.68, m, 4H, CCH<sub>2</sub>; 1.88 – 2.15, m, 4H, CCH<sub>2</sub>; 2.72 – 3.08, m, 4H, 3H from  
NCH<sub>3</sub> and 1H from NCH; 3.28, s, 3H, NCH<sub>3</sub>; 3.40 – 3.72, m, 2H, 1H from NCH and 1H  
from SCH<sub>2</sub>; 4.25, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.27, d, J=5 Hz, 1H,  $\beta$ -  
lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.94, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 8.06, s,  
25 1H, CH=N; 9.85, d, J=8 Hz, 1H, NH
- 29 (500 MHz, CDCl<sub>3</sub>/CH<sub>3</sub>OD)  
0.82 - 0.88, m, 2H, CCH<sub>2</sub>; 1.32 – 2.14, m, 10H, CCH<sub>2</sub>; 2.68 – 2.82, m, 2H, NCH; 3.52 –  
3.72, m, 2H, 1H from SCH<sub>2</sub> and 1H from NCH; 4.12, part of the AB-quartet, J=18 Hz,  
30 1H, SCH<sub>2</sub>; 5.15, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.96, d, J=5 Hz,  
1H,  $\beta$ -lactam; 8.65, s, 1H, CH=N
- 30 1.10 – 1.68, m, 4H, CCH<sub>2</sub>; 1.72 – 2.00, m, 7H, 4H from CCH<sub>2</sub> and 3H from CH<sub>3</sub>; 3.32,  
s, 3H, NCH<sub>3</sub>; 3.40 – 3.70, m, 3H, 2H from NCH and 1H from SCH<sub>2</sub>; 4.56, part of the

AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.27, d, J=5 Hz, 1H, β-lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 8.09, s, 1H, CH=N; 9.85, d, J=8 Hz, 1H, NH

- 5    31    1.32 – 1.72, m, 4H, CCH<sub>2</sub>; 1.80 – 2.12, m, 4H, CCH<sub>2</sub>; 3.33, s, 3H, NCH<sub>3</sub>; 3.40 – 3.90, m, 3H, 2H from NCH and 1H from SCH<sub>2</sub>; 4.59, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H, β-lactam; 5.79, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.95, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 7.32 – 7.58, m, 3H, aromatic-H; 7.70 – 7.90, m, 2H, aromatic-H; 8.10, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH
- 10    32    1.25 – 1.70, m, 4H, CCH<sub>2</sub>; 1.75 – 2.08, m, 4H, CCH<sub>2</sub>; 2.18, s, 3H, CH<sub>3</sub>; 3.30, s, 3H, NCH<sub>3</sub>; 3.48 – 3.80, m, 3H, 2H from NCH and 1H from SCH<sub>2</sub>; 4.54, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H, β-lactam; 5.79, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.96, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 7.08 – 7.60, m, 4H, aromatic-H; 8.08, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH
- 15    33    1.28 – 1.68, m, 4H, CCH<sub>2</sub>; 1.75 – 2.02, m, 4H, CCH<sub>2</sub>; 3.31, s, 3H, NCH<sub>3</sub>; 3.48 – 3.75, m, 3H, 2H from NCH and 1H from SCH<sub>2</sub>; 4.20, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 4.50, s, 2H, NCH<sub>2</sub>; 5.11, d, J=5 Hz, 1H, β-lactam; 5.66, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 6.82 – 7.02, m, 3H, aromatic-H; 7.22 – 7.40, m, 2H, aromatic-H; 8.08, s, 1H, CH=N; 9.75, d, J=8 Hz, 1H, NH
- 20    34    1.15 – 1.55, m, 4H, CCH<sub>2</sub>; 1.58 – 1.90, m, 4H, CCH<sub>2</sub>; 2.05, s, 3H, CH<sub>3</sub>; 2.75 – 3.05, m, 1H, NCH; 3.25, s, 3H, NCH<sub>3</sub>; 3.32 – 3.68, m, 2H, 1H from NCH and 1H from SCH<sub>2</sub>; 4.50, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H, β-lactam; 5.77, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.96, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 7.65 – 7.90, m, 4H, aromatic-H; 8.05, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH
- 25    35    1.15 – 1.68, m, 4H, CCH<sub>2</sub>; 1.72 – 2.05, m, 4H, CCH<sub>2</sub>; 3.25 – 3.72, m, 8H, 3H from NCH<sub>3</sub>, 2H from NCH, 2H from NCH<sub>2</sub> and 1H from SCH<sub>2</sub>; 4.20, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.12, d, J=5 Hz, 1H, β-lactam; 5.70, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 5.76, d, J=55 Hz, 2H, CH<sub>2</sub>F; 6.80 – 7.00, m, 2H, thiophenyl-H; 7.30 – 7.40, m, 1H, thiophenyl-H; 8.08, s, 1H, CH=N; 9.76, d, J=8 Hz, 1H, NH
- 30

- 36 1.30 – 1.78, m, 4H, CCH<sub>2</sub>; 1.88 – 2.12, m, 4H, CCH<sub>2</sub>; 2.64, s, 3H, SCH<sub>3</sub>; 2.90 – 3.18, m, 1H, NCH; 3.52 – 3.72, m, 4H, 3H from NCH<sub>3</sub> and 1H from SCH<sub>2</sub>; 3.88 – 4.12, m, 1H, NCH; 4.32, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 5.30, d, J=5 Hz, 1H, β-lactam; 5.77, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.98, dd, J=5 Hz and 8 Hz, 1H, β-lactam; 8.38, s, 1H, CH=N; 9.88, d, J=8 Hz, 1H, NH
- 5
- A1 1.10 – 1.60, m, 4H, CCH<sub>2</sub>; 1.72 – 2.12, m, 4H, CCH<sub>2</sub>; 2.75 – 3.08, m, 1H, NCH; 3.30 – 3.60, m, 1H, NCH; 8.30, b, 3H, NH
- 10 A2 1.08 – 2.20, m, 8H, CCH<sub>2</sub>; 3.00 – 3.28, m, 1H, NCH; 3.60 – 3.88, m, 1H, NCH; 7.72, b, 2H, NH; 8.48, b, 3H, NH
- A3 1.00 – 2.20, m, 8H, CCH<sub>2</sub>; 2.78, s, 3H, NCH<sub>3</sub>; 3.05 – 3.32, m, 1H, NCH; 3.60 – 3.85, m, 1H, NCH; 8.50, b, 3H, NH
- 15 A4 1.25 – 1.65, m, 4H, CCH<sub>2</sub>; 1.70 – 2.20, m, 4H, CCH<sub>2</sub>; 2.70 – 3.08, m, 4H, 3H from NCH<sub>3</sub> and 1H from NCH; 3.35 – 3.65, m, 1H, NCH; 8.35, b, 3H, NH
- A5 1.00 – 2.20, m, 8H, CCH<sub>2</sub>; 2.78, s, 3H, NCH<sub>3</sub>; 3.05 – 3.32, m, 1H, NCH; 3.60 – 3.85, m, 1H, NCH; 8.50, b, 3H, NH
- B1 1.12 – 1.55, m, 4H, CCH<sub>2</sub>; 1.75 – 1.98, m, 4H, CCH<sub>2</sub>; 2.30, b, 6H, NCH<sub>3</sub>; 2.70, s, 3H, NCH<sub>3</sub>; 3.20 – 3.80, m, 2H, NCH
- 20 B2 (D<sub>2</sub>O) 1.22 – 1.70, m, 4H, CCH<sub>2</sub>; 1.90 – 2.28, m, 4H, CCH<sub>2</sub>; 2.70, b, 6H, NCH<sub>3</sub>; 2.95 – 3.45, m, 2H, NCH
- B3 1.10 – 1.88, 6H, CCH<sub>2</sub>; 1.90 – 2.18, m, 2H, CCH<sub>2</sub>; 2.37, s, 3H, NCH<sub>3</sub>; 2.76, s, 3H, NCH<sub>3</sub>; 2.83, s, 3H, NCH<sub>3</sub>; 3.32 – 3.62, m, 2H, NCH
- 25 C1 1.40 – 1.70, m, 4H, CCH<sub>2</sub>; 1.82 – 2.30, m, 4H, CCH<sub>2</sub>; 2.80, s, 3H, NCH<sub>3</sub>; 3.05, b, 9H, NCH<sub>3</sub>; 3.30 – 3.50, m, 1H, NCH; 3.60 – 3.80, m, 1H, NCH
- C2 1.18 – 1.70, m, 4H, CCH<sub>2</sub>; 1.88 – 2.30, m, 4H, CCH<sub>2</sub>; 3.05, b, 9H, NCH<sub>3</sub>; 3.20 – 3.68, m, 2H, NCH
- 30 D1 (D<sub>2</sub>O) 1.20 – 1.60, m, 8H, CCH<sub>2</sub>; 1.80 – 2.18, m, 8H, CCH<sub>2</sub>; 2.95 – 3.20, 5H, 3H from NCH<sub>3</sub> and 2H from NCH; 3.22 – 3.48, m, 2H, NCH
- D1 1.25 – 1.60, m, 4H, CCH<sub>2</sub>; 1.82 – 2.18, m, 4H, CCH<sub>2</sub>; 3.00 – 3.20, 4H, 3H from NCH<sub>3</sub> and 1H from NCH; 3.22 – 3.45, m, 1H, NCH

**D2 - D5, D8**

1.10 – 2.25, m, 8H, CCH<sub>2</sub>; 2.88 – 3.12, m, 1H, NCH; 3.20, s, 3H, NCH<sub>3</sub>; 3.52 – 3.85, m, 1H, NCH; 7.75, b, 2H, NH; 8.40, b, 3H, NH

5     **D6** (D<sub>2</sub>O) 1.25 – 1.60, m, 4H, CCH<sub>2</sub>; 1.82 – 2.18, m, 4H, CCH<sub>2</sub>; 3.00 – 3.20, 4H, 3H from NCH<sub>3</sub> and 1H from NCH; 3.22 – 3.45, m, 1H, NCH

**D7** (D<sub>2</sub>O) 1.50 – 1.90, m, 8H, CCH<sub>2</sub>; 3.09, s, 3H, NCH<sub>3</sub>; 3.20 – 3.40, m, 1H, NCH; 3.50 – 3.68, m, 1H, NCH

10     **E1** 1.35 – 1.72, m, 4H, CCH<sub>2</sub>; 1.82 – 2.30, m, 4H, CCH<sub>2</sub>; 3.05, b, 9H, NCH<sub>3</sub>; 3.20, s, 1H, NCH<sub>3</sub>; 3.30 – 3.72, m, 2H, NCH; 7.45, d, J=4 Hz, 1H, NH; 7.74, b, 2H, NH

**H1** 1.30 – 1.65, m, 4H, CCH<sub>2</sub>; 1.78 – 2.15, m, 4H, CCH<sub>2</sub>; 2.70 – 3.00, m, 4H, 3H from NCH<sub>3</sub> and 1H from NCH; 3.14, s, 3H, NCH<sub>3</sub>; 3.22 – 3.55, m, 1H, NCH; 8.19, b, 3H, NH

15     **H2** (DMSO-d<sub>6</sub>/D<sub>2</sub>O) 1.20 – 1.50, m, 4H, CCH<sub>2</sub>; 1.78 – 2.02, m, 4H, CCH<sub>2</sub>; 2.80 – 3.10, m, 1H, NCH; 3.40, s, 3H, NCH<sub>3</sub>; 3.80 – 4.05, m, 1H, NCH

**H3** 1.00 – 1.92, m, 17H, 9H from CCH<sub>3</sub> and 8H from CCH<sub>2</sub>; 2.56, s, 3H, SCH<sub>3</sub>; 3.00 – 3.25, m, 1H, NCH; 3.51, s, 3H, NCH<sub>3</sub>; 3.68 – 3.92, m, 1H, NCH

20     **G1** 1.10 – 1.40, m, 4H, CCH<sub>2</sub>; 1.50 – 1.80, m, 4H, CCH<sub>2</sub>; 2.65 – 2.90, m, 1H, NCH; 3.10, s, 3H, NCH<sub>3</sub>; 3.20 – 3.50, m, 1H, NCH; 6.85, d, J=4 Hz, 2H, aromatic-H; 7.52, d, J=4 Hz, 2H, aromatic-H

25     **I1** 1.00 – 1.50, m, 13H, 9H from CCH<sub>3</sub> and 4H from CCH<sub>2</sub>; 1.60 – 1.90, m, 4H, CCH<sub>2</sub>; 3.08, s, 3H, NCH<sub>3</sub>; 3.25 – 3.80, m, 2H, NCH

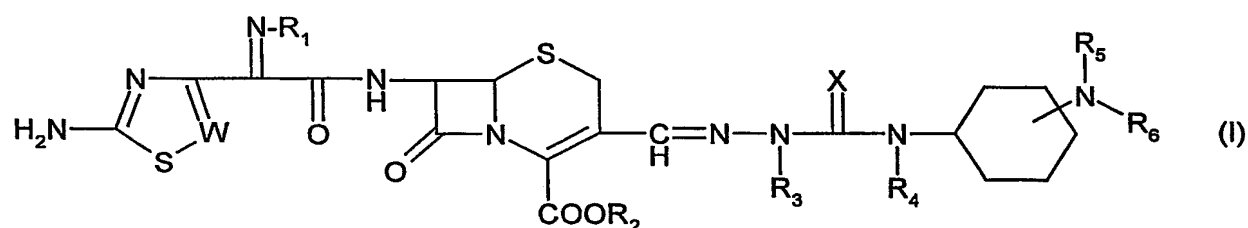
**F1** (D<sub>2</sub>O) 0.88 – 1.75, m, 6H, 4H from CCH<sub>2</sub> and 3H from CCH<sub>3</sub>; 1.80 – 2.35, m, 4H, CCH<sub>2</sub>; 2.90 – 3.70, m, 4H, 2H from NCH<sub>2</sub> and 2H from NCH

30     **F2** (D<sub>2</sub>O) 1.20 – 1.65, m, 4H, CCH<sub>2</sub>; 1.80 – 2.22, m, 4H, CCH<sub>2</sub>; 3.00 – 3.20, m, 1H, NCH; 3.22 – 3.52, m, 1H, NCH; 3.88 – 4.20, m, 2H, NCH<sub>2</sub>; 4.98 – 5.40, m, 2H, C=CH<sub>2</sub>; 5.55 – 5.88, m, 1H, CH=C



**Patent claims:**

1. A compound of formula



wherein

W is CH or N,

R<sub>1</sub> is hydrogen, hydroxy, (C<sub>1-6</sub>)alkoxy, halo(C<sub>1-6</sub>)alkoxy, hydroxycarbonyl(C<sub>1-6</sub>)alkoxy or (C<sub>1-6</sub>)alkyloxycarbonyl(C<sub>1-6</sub>)alkoxy,

R<sub>2</sub> is hydrogen or an ester moiety,

R<sub>3</sub> is hydrogen, (C<sub>1-6</sub>)alkyl, allyl or cyclo(C<sub>3-8</sub>)alkyl,

R<sub>4</sub> is hydrogen or methyl,

R<sub>5</sub> and R<sub>6</sub> independently from each other are hydrogen, (C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkylcarbonyl, arylcarbonyl, aryl(C<sub>1-6</sub>)alkylcarbonyl, heteroaryl(C<sub>1-6</sub>)alkylcarbonyl, (C<sub>1-6</sub>)alkylsulfonyl, arylsulfonyl or aryl(C<sub>1-6</sub>)alkylsulfonyl, and

X is N-R<sub>8</sub>, O, S, O-R<sub>8</sub> or S-R<sub>8</sub> wherein R<sub>8</sub> is hydrogen, (C<sub>1-6</sub>)alkyl, cyclo(C<sub>3-8</sub>)alkyl or aminocyclo(C<sub>3-8</sub>)alkyl.

2. A compound according to claim 1 of formula I wherein

W is CH or N,

R<sub>1</sub> is hydroxy, methoxy, fluoromethoxy, hydroxycarbonylmethoxy or hydroxycarbonylisopropoxy,

R<sub>2</sub> is hydrogen,

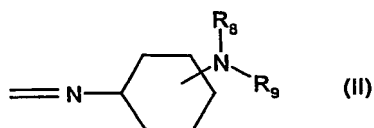
R<sub>3</sub> is hydrogen, methyl, allyl or cyclopropyl,

R<sub>4</sub> is hydrogen or methyl,

R<sub>5</sub> and R<sub>6</sub> independently from each other are hydrogen, methyl, phenylcarbonyl, aryl substituted by acetyloxy, phenyloxyacetyl, phenylsulfonyl substituted by amino or acetyl amino, 1-thiophene-2-yl-acetyl or cyclohexyl substituted by amino, and

X is NH, NCH<sub>3</sub>, O, S, S-(C<sub>1-6</sub>)alkyl or a group of formula

- 31 -



wherein  $R_8$  and  $R_9$  are defined as  $R_5$  and  $R_6$ .

3. A compound according to claim 1 or 2 in the form of a salt.

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4. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3 in association with at least one pharmaceutical excipient.

5. Use of a compound according to any one of claims 1 to 3 as a pharmaceutical.

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6. Use according to claim 5 in the treatment of microbial diseases.

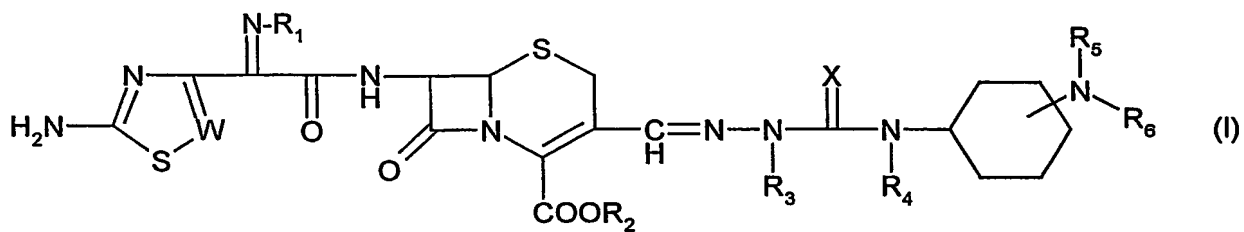
7. A method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of a compound according to any one of claims 1 to 4.

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IL/14-Oct-2002

Abstract:

A compound of formula



wherein the substituents have various meanings, useful as a pharmaceutical.